Clinical Relevance of HER-2/neu Overexpression in Patients With Testicular Nonseminomatous Germ Cell Tumor

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Introduction: Recent scientific attention has focused on the role of growth factors in the progression of cancer. HER-2/neu is an epidermal growth factor receptor that is demonstrated to have correlation with poor prognosis of many cancers. This study evaluated the overexpression of HER-2/neu protein and its clinical importance in nonseminomatous germ cell tumors of the testis.

Materials and Methods: Testis specimens of 54 patients with testicular nonseminomatous germ cell tumors, referred to Omid Hospital from 2001 to 2007, were re-evaluated and the patients' records were reviewed. Patients' age, tumor subtype, tumor stage, tumor markers, therapeutic response, and disease-free survival were assessed and the specimens were evaluated for the degree of HER-2/neu expression using an immunohistochemistry method.

Results: Immunohistochemical staining was performed for 54 specimens. Overexpression of HER-2/neu was seen in 33.3% of the patients with nonseminomatous germ cell tumors, especially in those with teratocarcinoma subtype compared to those with mixed germ cell tumors or embryonal cell carcinoma. However, HER-2/neu overexpression did not show any correlation with tumor stage, therapeutic response, disease-free survival, age, β-human chorionic gonadotropin, or α-fetoprotein.

Conclusion: We observed overexpression of HER-2/neu receptor in teratocarcinoma subtype of germ cell tumor. We suggest further studies to evaluate the clinical importance of this finding.

Keywords: germ cell and embryonal neoplasms, neoplasm proteins, prognosis, tumor markers

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INTRODUCTION

Recent scientific attention has focused on the role of growth factors in the progression of cancer. HER-2/neu is an epidermal growth factor receptor (EGFR)—encoded by the *ERBB2* gene (formerly named *HER-2/neu*)—that is overexpressed on the cell surface of approximately 25% to 30% of breast cancers.[1] This expression correlates with a relatively poor prognosis for patients with breast cancer; it is associated with a shorter disease-free survival and overall survival.[2] HER-2/neu has proved to be a useful therapeutic target in many cancers. Treatment of patients with HER-2/neu-amplified tumors with trastuzumab, a monoclonal antibody, results in a better clinical response rate.[3] Overexpression of HER-2/neu has been reported in

many epithelial malignancies, including cancers of the lung, prostate, bladder, pancreas, and esophagus, as well as sarcoma.[4-13] However, there is no evidence so far that HER-2/neu expression is of prognostic relevance in these malignancies.

The potential role of HER-2/neu in germ cell tumors (GCTs) is unknown. Some recent studies have tested these tumors immunohistochemically with monoclonal anti-HER-2/neu antibody.[14] The objective of our study was to determine the clinical importance of HER-2/neu protein overexpression in GCTs.

MATERIALS AND METHODS

We studied 54 patients with documented testicular nonseminomatous GCT referred to Omid Hospital between 2001 and 2007. Pathology specimens were collected and the patients' records were reviewed. Patients' age, tumor subtype, tumor stage, therapeutic response, tumor markers, and disease-free survival were assessed and the specimens were evaluated for the degree of HER-2/neu expression by immunohistochemistry methods (HercepTest kit, Dako, Carpinteria, California, USA), according to the manufacturer's instructions. A pathologist who was unaware of tumor type evaluated all immunohistochemistry specimens. The staining intensity was scored from 0 to 3+ using the breast cancer HER-2/neu scoring system,[1] with 2+ or 3+ staining considered positive for protein overexpression.

Patients with and without HER-2/neu overexpression were compared in terms of tumor characteristics, outcome, and tumor markers using the *t* test and the chi-square test, where appropriate. Continuous variables were shown as mean ± standard deviation. *P* values less than .05 were considered significant.

RESULTS

Immunohistochemical staining was performed in 54 testis specimens of patients with documented nonseminomatous GCT. Results of the test are shown in Table 1. HER-2/neu overexpression was reported in 18 specimens (33.3%). A positive overexpression was more prominent in cases of teratocarcinoma, but stage of the tumor and the response to treatment were not linked with HER-2/neu expression (Table 2). The frequency of HER-2/neu overexpression in tumor subtypes of different stages is demonstrated in Table 3. HER-2/neu overexpression was associated with a lower level of lactate dehydrogenase ($P = .006$), but it was not linked with the other tumor markers (Table 4).

Table 1. HER-2/neu Expression in Patients With Nonseminomatous Germ Cell Tumor of Testis

HER-2/neu Expression	Patient (%)
Negative	15 (27.8)
1+	21 (38.9)
2+	15 (27.8)
3+	3 (5.6)

Table 2. Relation of HER-2/neu Overexpression With Tumor Characteristics and Outcome of Treatment in Patients With Nonseminomatous Germ Cell Tumor of Testis*

	HER-2/neu Overexpression		
Variable	No	Yes	*P*
Tumor subtype			
Embryonal cell	12 (92.3)	1 (7.7)	
Teratocarcinoma	3 (33.3)	6 (66.7)	
Mixed tumor	21 (65.6)	11 (34.4)	.02
Tumor stage			
I	11 (61.1)	7 (38.9)	
II	19 (76.0)	6 (24.0)	
III	6 (54.5)	5 (45.5)	.38
Response to treatment			
Cure	21 (63.6)	12 (36.4)	
Recurrence	8 (72.7)	3 (27.3)	.72

*Values in parentheses are percents.

Table 3. Relation of HER-2/neu Overexpression With Stage of Tumor Subtype in Patients With Nonseminomatous Germ Cell Tumor of Testis

	HER-2/neu Overexpression	
Tumor Stage	No	Yes
Embryonal cell		
I	1	0
II	8	0
III	3	1
Teratocarcinoma		
I	1	3
II	2	1
III	0	2
Mixed tumor		
I	8	4
II	8	6
III	4	2

Table 4. Disease-free Survival Time, Age, and Tumor Markers in Patients With and Without HER-2/neu Overexpression

Parameter	HER-2/neu Overexpression		*P*
	No	Yes	
Disease-free, mo	20.77 ± 32.09	24.94 ± 22.28	.58
Age, y	28.47 ± 9.21	25.83 ± 11.90	.37
β-human chorionic gonadotropin, mU/mL	1505.49 ± 7672.56	240.35 ± 373.76	.49
α-fetoprotein, ng/mL	184.37 ± 341.88	441.38 ± 1268.53	.26
Lactate dehydrogenase, U/L	658.77 ± 999.80	253.44 ± 633.26	.006

Follow-up duration ranged from 2 to 91 months. The mean disease-free survival time was not significantly different between the patients with and without HER-2/neu overexpression (Table 4).

DISCUSSION

The recent availability of targeted therapy with tyrosine kinase inhibitors, particularly with agents directed against EGFR, offers new hope for effective and better tolerated therapy for human neoplasms. We designed a preliminary study evaluating the expression of HER-2/neu among nonseminomatous GCTs.

The expression of EGFR has been previously evaluated in primary GCTs. Shuin and associates reported the expression of EGFR at the transcriptional level in 2 of 3 immature teratomas, but no expression could be demonstrated in 15 seminomas and 6 embryonal carcinomas.[15] Moroni and colleagues evaluated the expression of EGFR by immunohistochemistry in a series of 24 testicular tumors. The expression of EGFR appeared to be restricted to the β-human chorionic gonadotropin (β-HCG)-positive component (choriocarcinoma) in 16 of 18 primary nonseminomatous GCTs. In contrast, 1 Leydig cell tumor, 5 seminomas, and β-HCG-negative components of GCTs did not express EGFR.[16] Recently, Kollmannsberger and coworkers evaluated the expression of EGFR by immunohistochemistry in a series of 22 patients with platinum-resistant GCTs and 12 patients with chemosensitive GCTs. They reported that the presence of EGFR was restricted to trophoblastic giant cells and the syncytiotrophoblastic elements of 4 nonseminomas, including 1 pure choriocarcinoma, and to a secondary non-germ-cell malignancy arising from a transformed teratoma. There were no differences in the pattern of EGFR expression between platinum-resistant and platinum-sensitive patients.[17]

In the present study, we found overexpression of HER-2/neu in 33.3% of the patients with nonseminomatous GCTs, especially in those with teratocarcinoma subtype. Our experience with agents targeting EGFR did not show any correlation between tumor stage or therapeutic response and the degree of expression of HER-2/neu. The mean disease-free survival, age, β-HCG, and α-fetoprotein were almost similar between the two groups of patients with and without HER-2/neu overexpression. In our study and several other previous investigations, the overexpression of HER-2/neu in teratocarcinoma was more frequently observed compared to mixed GCTs or embryonal cell carcinoma. Mandoky and colleagues also studied clinical relevance of HER-2/neu expression in germ cell testicular tumors in 2004, and they reported that teratomatous and choriocarcinoma components showed significantly higher HER-2/neu expression compared to other histological subtypes of GCTs.[18] Mandoky and colleagues also studied expression of HER-2/neu in testicular tumors in 2003 and showed that overexpression of HER-2/neu was restricted to the more differentiated histotypes.[19]

In our cohort, there was no significant correlation between expression of HER-2/neu and β-HCG, α-fetoprotein, patient survival, or age. However, some investigators such as Soule and colleagues who studied HER-2/neu expression in GCTs have reported that overexpression of the HER-2/neu protein in GCTs is of prognostic or therapeutic relevance.[20] Mandoky and colleagues also reported that HER-2/neu overexpression was associated with an adverse clinical outcome and had a prognostic role in testicular GCTs.[18] Some

other studies showed the correlation between HER-2/neu overexpression and histological subtype (teratocarcinoma), but they could not demonstrate the exact clinical importance of this finding. The reason might be the small sample volume that would limit further interpretations about clinical factors.[14] Thus, we suggest further investigations with more cases and with prolonged follow-up to evaluate clinical role of HER-2/neu expression in predicting disease course and treatment outcome. We suggest studies especially focused on teratocarcinoma with overexpression of HER-2/neu receptor in order to find a practical and clinical predictor factor for treatment planning.

CONCLUSION

We observed overexpression of HER-2/neu receptor in teratocarcinoma subtype of GCT. We suggest further studies to evaluate the clinical importance of this finding.

CONFLICT OF INTEREST

None declared.

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